

HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): a randomised controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible after dentoalveolar surgery

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**Trial registration: European Clinical Trials Database, ID: EudraCT200700622527**

**Brief Title:** HBO for the Prevention of Osteoradionecrosis

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**Contributors:**

RS was the chief investigator of the trial, was involved in study design, was responsible for the clinical supervision of patients and performance of the study and contributed to the preparation and writing of the report. CB, AK, PN, JM, PP, TL, MBG, LF, PB, RP, GS, RS, TC and MG were study investigators responsible for patient recruitment, clinical supervision, and treatment of patients, were involved in the acquisition, analysis, and interpretation of the data, and contributed to the writing of the report. BT and MB were trial co-ordinators and were responsible for data collection, and were involved in the acquisition, analysis, and interpretation of the data, and contributed to the writing of the report. PS & RJ were responsible for the acquisition and analysis of the data and contributed to the writing of the report.

All authors have approved the final article.

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**Abstract****Purpose:**

Hyperbaric oxygen (HBO) has been advocated in the prevention and treatment of osteoradionecrosis of the jaws following head and neck radiotherapy, but supporting evidence is weak. The aim of this randomized trial was to establish the benefit of HBO in prevention of osteoradionecrosis following high risk surgical procedures to the irradiated mandible.

**Methods and Materials:**

XXXXXX was a randomized controlled phase 3 trial. Participants were recruited who required dental extractions or implant placement in the mandible with prior radiotherapy >50Gy. Eligible patients were randomly assigned (1:1) to receive, or not receive HBO. All patients received chlorhexidine mouthwash and antibiotics. For patients in the HBO arm, oxygen was administered in 30 daily dives at 100% oxygen to a pressure of 2.4 ATA for 80-90 minutes. The primary outcome measure was the diagnosis of osteoradionecrosis six months following surgery as determined by a blinded central review of clinical photographs and radiographs. Secondary endpoints included grade of osteoradionecrosis, osteoradionecrosis at other time-points, acute symptoms, pain and quality of life.

**Results:**

144 patients were randomised, and 100 were analysed for the primary endpoint. The incidence of osteoradionecrosis at 6 months was 6.4% and 5.7% for the HBO and control

groups respectively, OR 1.13,  $P = 1$  (95% CI: 0.14 to 8.92). Patients in the hyperbaric arm had fewer acute symptoms but no significant differences in late pain or quality of life. Drop-out was higher in the HBO arm, but baseline characteristics of groups completing the trial were comparable between the two arms.

#### Conclusions:

The low incidence of osteoradionecrosis seen makes it unnecessary to recommend HBO for dental extractions or implant placement in the irradiated mandible. These findings are in contrast to a recently published Cochrane review and previous trials reporting rates of ORN (non-HBO) of 14-30%, and challenge a long-established standard of care.

## Introduction

Osteoradionecrosis (ORN) is exposed necrotic bone following radiotherapy in the absence of cancer recurrence(1,2). Mandibular ORN is a common complication of head and neck radiotherapy causing pain, infection and malnutrition. The incidence of head and neck malignancy and use of radiotherapy is rising(3), as is survival(4), thus the at-risk population for ORN is increasing.

The risk of ORN is higher in the posterior mandible and if more than 60 Gray has been received(5,6). In order to prevent ORN, dental health is optimized prior to radiotherapy(7), however dental surgery such as extractions or implant placement is often indicated. The risk of such procedures in precipitating ORN is unknown but has been reported as 20-30%(6,8). The overall cumulative incidence of spontaneous ORN may have reduced with the adoption of intensity modulated radiotherapy(9,10), but the specific risk to patients caused by dental procedures is less clear.

The role of hyperbaric oxygen (HBO) in the prevention of mandibular ORN following dental procedures remains controversial(11,12). Marx's randomized controlled trial(8) showed a lower incidence of ORN after dental extractions with HBO (5.4%) than when treated with penicillin (29.9%) . Vudiniabola et al(13) showed that of 29 patients who received HBO, one (3.4%) developed ORN; and of 7 patients who did not receive HBO, one (14.3%) developed ORN. Prophylactic HBO became a standard of care for high risk dental extractions(14) on the basis of this limited evidence. Other trials have not demonstrated benefit for HBO in the treatment of established mandibular ORN(15), or in late radiation toxicities to other

anatomical sites(16). Similarly, controversy surrounds the role of HBO in the placement of implants in the irradiated mandible, where there is conflicting evidence(17,18) from retrospective series. The costs and logistic arrangements implicit in 30 daily treatments with HBO present a barrier to universal adoption. In a recent Cochrane review(19), it was concluded that HBO reduced the chance of ORN following a tooth extraction, but stressed the need for further well designed studies.

In order to address the paucity of evidence, we conducted the XXXXXX trial. The aim of this randomized trial was to establish the benefit of HBO in prevention of ORN following high-risk surgical procedures to the irradiated mandible. Additionally, the XXXXXX trial aimed to define the changes in acute symptoms accompanying surgery, long-term pain and quality of life resulting from use of HBO, as well as to determine the risk of ORN.

## Methods

The XXXXXX trial was a randomized controlled phase III study. The patients and site investigators were unblinded, but assessment of the primary endpoint was blinded, as it was remotely assessed by a blinded expert panel of investigators. The trial was conducted in 16 acute UK hospitals, one acute hospital in Denmark, and nine UK hyperbaric medicine facilities registered with the British Hyperbaric Association. The XXXXXX trial protocol was granted ethical approval by Greater Manchester Central Research Ethics Committee (REC reference 08/H1008/32). The study protocol is available at [XXXXXXX](#) and a more detailed description has been published(20). The phase III analysis incorporates data from the preceding XXXXXX phase II feasibility study with parallel trial inclusion, randomisation, procedures and assessments for the first 48 randomised patients.

### Participants

Eligible participants were men and women aged 18 years or older with an indication for surgery to the mandible and prior radiotherapy to the mandible of at least 50Gy. Indications for surgery included extraction of premolar or molar teeth or the placement of osseointegrated dental implants.

### Randomisation

Eligible patients were randomly assigned (1:1) to receive, or not receive HBO. Allocation of treatment was unblinded to site investigators and patients.

### Procedures



Patients in both arms of the trial were given chlorhexidine mouthwash and antibiotics. Pre- and post-operative chlorhexidine mouthwash 0.2% was used in a volume of 10ml rinsed around the mouth for around 1 minute and spat out, three times daily for 5 days post-operatively. Orally administered antibiotics comprised amoxicillin 3g one hour pre-operatively, or 1g administered intravenously, and 250mg three times daily for 5 days post-operatively. Suitable alternatives were used to substitute for chlorhexidine or amoxicillin in the case of allergy. For patients in the HBO arm, oxygen was administered at 2.4 ATA for 80-90minutes, in 30 daily treatments, 20 immediately prior to and 10 after surgery. The trial procedures are summarised in figure 1. For those patients who developed ORN, their subsequent management was not specified in the trial protocol, however the grade of ORN was followed to the 12 month timepoint.

## Outcomes

The primary outcome measure was the presence or absence of osteoradionecrosis (ORN) six months following surgery, determined by a blinded central review of clinical photographs and radiographs and classified using the modified Notani score(1,20,21) (supplementary table 1). The secondary endpoints were: ORN similarly assessed at three and twelve months; pain; and quality of life. Additionally, acute symptoms (pain, swelling, trismus and diet) were self-recorded during the first week following surgery.

## Sample Size - Stopping Rules

The incidence of ORN in the control arm was anticipated to be 18-19%, as evidenced by prior trials such as those of Marx et. al.(8) and Vudiniabola et. al.(13) who reported comparable rates of 30% and 14% respectively. Based on this, 103 evaluable patients per

group would provide 80% power to detect an odds ratio of 0.23, equating to a rate of 18.5% in the control arm and 5% in the HBO treatment arm, with a difference of 13.5%. Estimating the dropout rate at 7%, planned recruitment was 221 patients. A single interim analysis was planned when 100 patients had been followed up for 6 months, using the Peto stopping rule for the primary efficacy outcome.

### Statistical Analysis

For the patients in the HBO arm, the additional treatment prior to surgery risked higher drop out than in the standard arm. The full analysis set used for the primary analyses was therefore defined as all randomised patients who had received surgery according to the treatment group originally allocated. The validity of this approach was supported by a range of sensitivity analyses. The primary test of efficacy was performed using a Fisher's exact test with exact logistic regression used to obtain exact 95% confidence intervals about an odds ratio. The null hypothesis was that HBO treatment was not more effective than standard care, i.e. the odds ratio was not statistically different from 1, while the alternate hypothesis was that HBO treatment was superior with an odds ratio of 0.23 or less. A two-sided test, with P-value of less than 0.05 was declared statistically significant. Significance tests for secondary endpoints were two-sided at 5% accompanied by 95% two-sided confidence intervals.

An Independent Safety Data Monitoring Committee oversaw the XXXXXX trial.

## Results

144 patients were randomized between 2008 and 2016, 72 (50%) into the HBO arm and 72 (50%) into the non-HBO arm. Drop-out after randomization, but prior to treatment, was higher in the HBO arm, with 17/72 (24%), compared with 6/72 (8%) in the non-HBO arm. 19 (13%) patients withdrew from study between surgery and the primary endpoint, 7/72 (10%) in the HBO arm and 12/72 (17%) on the non-HBO arm. One patient in each arm was determined to be ineligible on review and there was a total of 100 patients available for the primary analysis with 47 in the HBO arm and 53 in the non-HBO arm (Figure 2). A further seven patients, four on HBO and three on non-HBO withdrew from the study after providing data on the primary outcome. Despite the differences in drop-out rate, the baseline characteristics were similar whether the comparison was made on those randomized, per protocol, or those analyzed for the primary endpoint (Table 1).

The overall incidence of ORN at the primary endpoint was 6/100 (6%), 3/47 (6.4%) in the HBO arm and 3/53 (5.7%) in the non-HBO arm. The odds ratio for ORN was 1.13, two-sided Fishers Exact  $P > 0.99$  (95% CI: 0.14 to 8.92). For patients undergoing dental extractions, the odds ratio was 0.72, two-sided Fishers Exact  $P > 0.99$  (95% CI: 0.06 to 6.66). The unblinded site investigators' assessment of ORN at 6 months also showed no difference; odds ratio = 1.02, two-sided Fishers Exact  $P > 0.99$  (95% CI: 0.31 to 3.27). The IDMC recommended closing the trial after 100 evaluable patients as the rate of ORN seen was much less than that assumed, precluding statistically significant efficacy analyses for HBO.

The incidence of ORN at 3 months was 7%, 3/45 (7%) on the HBO arm and 4/55 (7%) on the non-HBO arm [OR 0.91 (two sided Fishers exact  $P > 0.99$  CI 0.13 to 5.72)]. None of the patients with ORN at 6-month primary endpoint had healed by 12 months, with the exception that one was lost to follow-up between these timepoints. No new ORN developed between 6 and 12 months. The grade of ORN at 6 months was Notani grade 1: 2 patients, Notani grade 2: 1 patient, Notani grade 3: 3 patients. Of the 100 patients available for analysis, 16 (16%) had no dental extraction with a single case of ORN (6%), 17 patients had a single extraction during surgery and two of these patients had ORN (11%) and 67 (67%) had multiple extractions with 3 (4%) of these patients experiencing ORN. The difference in ORN between extraction status was not statistically significant ( $p = 0.558$ ).

The incidence of minor bone spicules (MBS) at the primary endpoint was 13%, 5/47 (10%) in the HBO arm and 8/53 (15%) in the non-HBO arm [odds ratio = 0.67, two-sided Fishers Exact  $P = 0.5642$  (95% CI: 0.16 to 2.55)]. MBS was managed entirely conservatively without sequestrectomy, and as all cases with MBS in the primary analysis had fully healed by 12 months, it is concluded this was by natural exfoliation.

Analysis of the acute symptoms questionnaire showed that, for area under the curve, patients had less severe symptoms in the first 7 days after surgery in the HBO arm for pain ( $P = 0.0458$ ), swelling ( $P = 0.0182$ ), bleeding ( $P = 0.0375$ ), mouth opening ( $P = 0.004$ ) and eating ( $P = 0.004$ ) (Table 2). The patients were unblinded to allocation, and these results reflect analysis of those 75% returning questionnaires (39 patients in the HBO arm, 36 patients in the non-HBO arm). A higher proportion (65%) of HBO arm patients were comfortable at day

8 post-surgery than in the non-HBO arm (35%) Exact OR 2.79, two sided-Fishers Exact  $P=0.038$  (95% C.I. 1.01 to 8.05).

Patients' experience of pain as assessed by visual analogue scores collected at baseline, 3,6 and 12 months are summarized in Table 3. Pain was lower in the HBO arm than non-HBO arm at all timepoints. However, the differences were small and of borderline statistical significance, and the absolute levels of pain were very low at 3,6 and 12 months. Pain scores reduced by 0.044 units per month in the non-HBO arm and 0.076 units in the HBO arm. These very small differences, i.e. less than 0.1 in the context of a 0-10 scale, are of doubtful clinical significance (Supplemental Table 2).

The measures of Quality of Life (QoL) in each arm were similar, with a marginal advantage for the HBO arm being partly attributable to a slight advantage at baseline. QOL data is presented as a summary of trend for composite physical score (Figure 3) and composite social score (Figure 4) for UW-QoL data obtained at baseline, 3-, 6- and 12-months. The changes in UW-QoL seen over the trial timepoints were modest and did not differ significantly between HBO and non-HBO arm.

Pain scores were very low, both for patients with full healing and for those with MBS; MBS: 0.1 (SD 0.22, 11 patients) versus Healed: 0.1 (SD 0.23, 81 patients). In contrast, mean pain was higher, at 0.3 (SD 0.3, 6 patients), for those patients with Notani grade 1,2 or 3 ORN. This data shows that the symptoms of those with MBS were more similar to healed

patients than those with ORN. The categorization of MBS with other healed patients appears to be justified.

For patients receiving dental implants, the loss of any implants was recorded beyond 12 months to date of trial closure. Implant survival post-surgery was high, 95% at 24 months (95% CI: 74% to 99%) and 83% at 48 months (95% CI: 48% to 95%). There were 13 implant failures amongst 4 patients, with 4 implants being lost in 1 patient in the HBO arm, and 9 implants in 3 patients in the non-HBO arm. The Hazard Ratio for implant loss in HBO versus non-HBO arms was 1.39; 95% CI 0.16 to 12.09,  $p=0.765$  (adjusted for clustering by patient).

Safety within the trial was good, and adverse events related to HBO tended to be of low grade. There were no significant differences in death, hospital admission, incapacitation or further surgery between the arms. Adverse events potentially attributable to HBO are shown in supplemental table 3. Serious adverse events were mostly related to subsequent malignancies, occurring in 13% of patients within 12 months. Recurrence of head and neck malignancy occurred in 4%, at a new site in 6%, and uncertain origin in 3%. There were no significant differences in the incidence of malignancy between the arms, with 7 diagnoses in 47 patients (15%) in HBO arm versus 6 in 53 patients (11%) in the non-HBO arm.

A range of sensitivity analyses was performed to explore any potential effect of drop-out on the primary endpoint (Supplemental Table 4). None provided any conclusive support for either benefit or harm and show the overall results of the study to be robust under a variety of assumptions.

## Discussion

The incidence of ORN in the XXXXXX trial was 6%, therefore the risk to irradiated patients needing dental procedures is too low to routinely justify the use of HBO, and also likely precluding future prevention trials in this setting. This finding is in itself highly significant, contradicting the findings of a recent Cochrane review(19). These results are in contrast with prior randomized trial evidence(8), but the overall incidence of ORN seen in the XXXXXX trial is consistent with a progressively declining trend reported in retrospective case series(22), cited as 7% in one recent study(9). Alternative methods for prophylaxis of ORN include the use of pentoxifylline and tocopherol. The single retrospective series(23) so far published confirms a very low rate of ORN, but reinforces the statistical challenges of powering randomized trials.

The low rate of ORN seen in the present data raises the question of whether subsequent surgery in the irradiated mandible, such as extraction or implant placement, actually causes additional cases of ORN, or merely changes the timing of presentation for cases that would have developed spontaneously. The XXXXXX trial clarifies the incidence and natural progression of ORN in a tightly controlled prospective study, adding significant data to a field dominated by anecdote and retrospective case series.

The reasons for the apparent reduction in risk of mandibular ORN may be attributable to more stringent dental protocols or more advanced, better targeted, radiotherapy techniques, such as intensity modulated radiotherapy (IMRT)(9,24). IMRT can effectively allow salivary glands to be spared with improvements in xerostomia(10), and it may also be

that it has reduced the impact of radiotherapy to the mandible in head and neck malignancy.

Regarding the secondary endpoints, there were significantly improved acute symptoms in the week following surgery in patients receiving HBO. There was slight less pain reported by patients in the HBO arm at three, six and twelve months, but these differences were too small to be of any clinical relevance. There were only minor and insignificant differences in QOL associated with the use of HBO. Taken as a whole, these symptomatic effects appear to be temporally related to the HBO sessions, reducing over time. These outcomes reflect unblinded analyses, so the differences may reflect placebo effect or a biological mechanism of HBO, which may reflect an anti-inflammatory or anti-infectious effect. It has been demonstrated that late radiation injury is usually accompanied by vascular atrophy, and lacks steep oxygen gradients required for angiogenesis in surgical wounds(25). This has been reversed in-vivo using 30 treatments of HBO and it is possible that such mechanisms might be able to improve symptoms in a dental extraction or implant wounds. In a comparable trial of HBO in late radiation tissue injury of the pelvis, the HORTIS trial(26) , showed early significant symptomatic benefits associated with HBO, but the subsequent HOT2 trial(16) showed no benefit at one year.

The strengths of the XXXXXX trial are mainly in the robust blinded nature of the primary endpoint assessment, and in the comparability between the two trial arms. The choice of 6 months as the primary endpoint appears justified, as ORN when seen at this time was stable. None of the patients with ORN at 6 months had healed by 12 months, and no new cases developed between 6 and 12 months.



The use of the category minor bone spicules (MBS) aided the primary analysis, and its distinction from ORN, is of critical importance. 13% of patients developed MBS at the primary endpoint which was more than double the incidence of ORN at 6%. The differences between MBS and ORN are clear in terms of severity, extent, symptoms and progression (Figures 5 and 6). All cases of MBS at the 6-month primary endpoint had spontaneously healed without intervention by 12 months whereas all cases of ORN at the primary endpoint persisted to 12 months. MBS was essentially asymptomatic, with comparable pain scores to those patients who had fully healed, whereas patients with ORN had more pain. The disparity in clinical appearance of ORN versus MBS is illustrated in Figures XXXX. MBS should, therefore, be regarded as clinically innocuous and reflects delayed healing rather than progressive bone necrosis. It is concerning that this entity has not been clearly characterized and accounted for in the data of previous trials and series in the field(1).

The current trial does not address the use of HBO in the management of established ORN, with or without surgical resection. Although this has been long-established, a previous prospective clinical trials did not find any benefit(15). A further trial led in Denmark by the DAHANCA group is underway exploring the role of HBO with surgical resection of ORN.

Several difficulties were encountered during the XXXXXX trial, particularly that of slow recruitment. In previous work within the portfolio of head and neck cancer trials(27), we had identified that where two arms of the trial appear very different in nature, many patients would be more likely express a preference for one or other arm. Similarly, as HBO has been a long-established standard of care in this setting, it may be that not all recruiting

clinicians were able to effectively convey equipoise(28). The unblinded nature of the data for assessment of acute symptoms, late pain and QOL means less weight can be attached to these secondary endpoints than the primary endpoint. In this regard the use of sham HBO as a 'placebo' arm, although not without inherent problems, would have aided the unbiased assessments of these more subjective endpoints.

An additional methodological concern was the high drop-out rate and disparity in drop-out rates between trial arms. The dropout rate was particularly high early in the trial and it was thought that some of these patients had not fully appreciated the logistic demands of HBO. This was addressed by reinforcing informed consent. Additionally, some trial sites unexpectedly withdrew funding when HBO was re-classified as a clinical trial excess treatment cost. There remained a higher propensity for drop-out in the HBO versus the non-HBO arm even after these issues were addressed, reflecting the longer time interval between randomization and treatment for the HBO arm. Despite this, demonstrable comparability between arms was retained, and a range of sensitivity analyses did not influence the primary analysis.

The XXXXXX trial confirms the safety of HBO in this patient population. The toxicities related to pressure effects and inspired oxygen percentage were much as expected. Previously, anecdotal concerns over the potential of HBO to reactivate otherwise dormant malignant cells have been raised for patients treated for late radiation effects. In the present trial, subsequent malignancies were notably common but there were no significant differences in incidence between the HBO and non-HBO trial arms.

In the light of the low incidence of ORN seen in the XXXXXX trial, amongst patients who had previously been considered at high risk, it is difficult to justify the future use of HBO in prevention of ORN associated with surgery or dental extraction in the irradiated mandible. These findings reverse the conclusions of the recently published Cochrane review in this clinical setting. Further, it would appear difficult to adequately power any subsequent ORN prevention trial unless a genuinely high-risk sub-set of patients could be identified, for example from biomarkers of susceptibility to severe late radiation effects(29,30). The significance of temporary improvements in symptoms attributable to the use of HBO remain uncertain, and this would require alternative trial designs to further explore. As the financial costs and logistic demands of HBO therapy are very high, the implications of this trial may include a significant economic saving for those health systems where HBO is currently considered a standard of care.

## References

1. REDACTED
2. Store G, Boysen M. Mandibular osteoradionecrosis: Clinical behaviour and diagnostic aspects. *Clin Otolaryngol Allied Sci* 2000;25:378-84.
3. Schache AG, Powell NG, Cuschieri KS, et al. Hpv-related oropharynx cancer in the united kingdom: An evolution in the understanding of disease etiology. *Cancer Res* 2016;76:6598-6606.
4. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
5. Lee IJ, Koom WS, Lee CG, et al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* 2009;75:1084-91.
6. Murray CG, Herson J, Daly TE, et al. Radiation necrosis of the mandible: A 10 year study. Part i. Factors influencing the onset of necrosis. *Int J Radiat Oncol Biol Phys* 1980;6:543-8.
7. Shaw RJ, Butterworth C. Hyperbaric oxygen in the management of late radiation injury to the head and neck. Part ii: Prevention. *Br J Oral Maxillofac Surg* 2011;49:9-13.
8. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 1985;111:49-54.
9. Caparrotti F, Huang SH, Lu L, et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. *Cancer* 2017;123:3691-3700.
10. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (parsport): A phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127-36.
11. Dhanda J, Hall TJ, Wilkins A, et al. Patterns of treatment of osteoradionecrosis with hyperbaric oxygen therapy in the united kingdom. *Br J Oral Maxillofac Surg* 2009;47:210-3.
12. Kanatas AN, Lowe D, Harrison J, et al. Survey of the use of hyperbaric oxygen by maxillofacial oncologists in the uk. *Br J Oral Maxillofac Surg* 2005;43:219-25.
13. Vudiniabola S, Pirone C, Williamson J, et al. Hyperbaric oxygen in the prevention of osteoradionecrosis of the jaws. *Aust Dent J* 1999;44:243-7.
14. Tong AC, Yan BS, Chan TC. Use of interdental distraction osteogenesis for orthodontic tooth alignment and correction of maxillary hypoplasia: A case report. *Br J Oral Maxillofac Surg* 2003;41:185-7.
15. Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: A randomized, placebo-controlled, double-blind trial from the orn96 study group. *J Clin Oncol* 2004;22:4893-900.
16. Glover M, Smerdon GR, Andreyev HJ, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (hot2): A randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncol* 2016;17:224-233.
17. Granstrom G. Osseointegration in irradiated cancer patients: An analysis with respect to implant failures. *J Oral Maxillofac Surg* 2005;63:579-85.

18. Shaw RJ, Sutton AF, Cawood JI, et al. Oral rehabilitation after treatment for head and neck malignancy. *Head Neck* 2005;27:459-70.
19. Bennett MH, Feldmeier J, Hampson NB, et al. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2016;4:CD005005.
20. REDACTED
21. Notani K, Yamazaki Y, Kitada H, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;25:181-6.
22. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: A systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:54-69.
23. Patel V, Gadiwalla Y, Sassoon I, et al. Prophylactic use of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of the head and neck. *Br J Oral Maxillofac Surg* 2016;54:547-50.
24. Ben-David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: Likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007;68:396-402.
25. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981;90:262-70.
26. Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: A randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008;72:134-143.
27. Kaur G, Hutchison I, Mehanna H, et al. Barriers to recruitment for surgical trials in head and neck oncology: A survey of trial investigators. *BMJ Open* 2013;3.
28. Rooshenas L, Elliott D, Wade J, et al. Conveying equipoise during recruitment for clinical trials: Qualitative synthesis of clinicians' practices across six randomised controlled trials. *PLoS Med* 2016;13:e1002147.
29. Ghazali N, Shaw RJ, Rogers SN, et al. Genomic determinants of normal tissue toxicity after radiotherapy for head and neck malignancy: A systematic review. *Oral Oncol* 2012;48:1090-100.
30. Lyons AJ, West CM, Risk JM, et al. Osteoradionecrosis in head-and-neck cancer has a distinct genotype-dependent cause. *Int J Radiat Oncol Biol Phys* 2012;82:1479-84.

**Table Legends**

Table 1 - Baseline characteristics of patients analyzed per protocol, i.e. completed allocated HBO, received surgery and followed up to 6-month primary endpoint assessment.

Table 2: Acute symptoms questionnaire, by trial arm.

These results reflect analysis of those 75% returning questionnaires (39 patients in the HBO arm, 36 patients in non-HBO arm). The p-values are from the joint structural equations model that includes Comfort at day 8; robust standard errors were used because of differences in variance and departures from Normality. Univariate Mann-Whitney p-values are also therefore displayed, in brackets.

Table 3: Visual analogue pain scores at each time point

**Figure titles**

Figure 1: XXXXX Trial Schema

Figure 2: Trial Consort diagram

Figure 3: UW-QoL Composite physical scores.

The physical subscale score is computed as an average of 6 domain scores: chewing, swallowing, speech, taste, saliva and appearance. A change of 12 units is deemed a large

change, one of 7.5 units a moderate. 0 represents the worst possible and 100 the best possible QoL.

Figure 4: UW-QoL Composite social-emotional scores.

The social-emotional subscale score is computed as an average of 6 domain scores: anxiety, mood, pain, activity, recreation, shoulder. A change of 12 units is deemed a large change, one of 7.5 units a moderate. 0 represents the worst possible and 100 the best possible QoL.

Figure 5: Clinical photograph of exposed bone: Minor Bone Spicules (MBS) – two areas of bone  $<20\text{mm}^2$  <sup>(1)</sup> in left posterior mandible 6 months after dental extraction. Minimal bone exposure subject to spontaneous exfoliation and subsequent healing by 12 months.

Figure 6: Clinical photograph of exposed bone: Notani grade 2 Osteoradionecrosis in right posterior mandible 12 months after molar tooth extraction. This area of exposed bone has progressed from Notani grade 1 at 6 months.

### Supplemental documents

Supplemental Table 1: Classification and definition of primary outcome in XXXXX trial

Supplemental Table 2: Linear mixed modelling of pain scores. Analysis of pain scores over the study are further analysed using a linear mixed modelling approach including a square root transformation on the observed pain score. A random intercept and slope model was applied, including fixed effects for treatment arm, time and the treatment by time

interaction. Change in pain score [mean (se)] reduced by 0.044 (0.044) pain units per month in the non-HBO arm and reduced by 0.076 (0.045) units per month in the HBO arm.

Supplemental Table 3: CTCAE toxicities within patients receiving HBO.

N(%) of patients with any adverse event related to HBO for all 58 patients receiving HBO; includes events occurring within 6 months of most recent HBO treatment.

Note: as recorded the SAE severity codes are 0 = Mild, 1 = Moderate, 2 = Severe; these have been aligned with the AE codes (the interpretation of an SAE severity of 3 or more is that this includes AE codes of 4 & 5 as well).

Supplemental Table 4: Summary of sensitivity analysis. Sensitivity analyses are performed under a range of differing assumptions for the primary outcome. Included are Sensitivity analysis where ORN is developed in line with the best and worst case scenarios (A and B) as well as scenarios in line with risk for development. For none of the analyses reported is there any notable deviation away from the reported Odds Ratio for the primary analysis [OR = 1.13 (0.14 – 8.92)]. Further sensitivity analyses were planned using multiple imputation to account for missing data but these results are not presented due to difficulties with model convergence.

Further to this, sensitivity analyses were performed to illustrate patterns of imputed outcomes where data are unavailable which would result in study interpretations which differ from those reported. Here, if it is assumed that the response rate is fixed at 6.4% in the missing data for the HBO group control arm, we would need to observe a ORN rate of 18% in the missing data of the standard care arm to determine statistical significance. If the



response rate is fixed at 3.2% in the missing data for the HBO group control arm, we would need to observe a ORN rate of 15% in the missing data of the standard care arm to determine statistical significance.

Characteristic (Reviewed patients)	HBO arm (47)	Control arm (53)	TOTAL (100)
Age yrs mean (SD)	58.3 (10)	58.2 (10.4)	58.2 (10.1)
Males, n(%)	14 (30%)	14 (27%)	28 (28%)
<b>Smoking, n(%)</b>			
Never	14 (29%)	17 (32%)	31 (31%)
Past	23 (48%)	26 (49%)	49 (49%)
Current	10 (21%)	10 (18%)	20 (20%)
Missing	0 (0%)	0 (0%)	0 (0%)
<b>Alcohol n(%)</b>			
Never	4 (12%)	3 (7%)	7 (10%)
Past	5 (15%)	10 (25%)	15 (21%)
Current	24 (72%)	26 (66%)	50 (69%)
Missing	14 (42%)	14 (35%)	28 (28%)
<b>Radiotherapy</b>			
Radiotherapy dose (Gy) mean (SD)	62.8 (7.8)	63 (10.2)	62.9 (9.1)
Radiotherapy duration (wks) mean (SD)	6.1 (1.6)	6.2 (1.7)	6.2 (1.7)

Table 1- Baseline characteristics of patients analysed per protocol, i.e. completed allocated HBO, received surgery and followed up to 6-month primary endpoint assessment.

Post-surgery Day	HBO pain	Standard pain	HBO swelling	Standard swelling	HBO bleeding	Standard bleeding	HBO opening mouth	Standard opening mouth	HBO eating	Standard eating
1	2.55 (SD = 1.17; N = 42)	2.92 (SD = 1.09; N = 37)	2.25 (SD = 1.03; N = 40)	2.65 (SD = 1.18; N = 37)	1.83 (SD = .97; N = 41)	2.3 (SD = 1.02; N = 37)	1.73 (SD = .99; N = 40)	2.58 (SD = 1.32; N = 36)	2.98 (SD = 1.42; N = 40)	4.03 (SD = 1.28; N = 32)
2	2.19 (SD = 1.06; N = 42)	2.7 (SD = 1.13; N = 37)	2.07 (SD = .96; N = 41)	2.59 (SD = 1.17; N = 37)	1.32 (SD = .57; N = 41)	1.7 (SD = .81; N = 37)	1.67 (SD = .84; N = 39)	2.56 (SD = 1.23; N = 36)	2.5 (SD = 1.4; N = 40)	3.85 (SD = 1.3; N = 33)
3	2.12 (SD = 1.09; N = 42)	2.43 (SD = 1.07; N = 37)	1.83 (SD = .8; N = 41)	2.38 (SD = .92; N = 37)	1.12 (SD = .4; N = 41)	1.44 (SD = .73; N = 36)	1.48 (SD = .75; N = 40)	2.49 (SD = 1.24; N = 37)	2.28 (SD = 1.36; N = 40)	3.68 (SD = 1.42; N = 31)
4	1.83 (SD = .93; N = 42)	2.16 (SD = .99; N = 37)	1.66 (SD = .76; N = 41)	1.95 (SD = .97; N = 37)	1.12 (SD = .4; N = 41)	1.28 (SD = .61; N = 36)	1.33 (SD = .62; N = 40)	2.16 (SD = 1.19; N = 37)	2.13 (SD = 1.42; N = 40)	3.36 (SD = 1.37; N = 33)
5	1.78 (SD = 1.08; N = 41)	2.16 (SD = 1.04; N = 37)	1.43 (SD = .64; N = 40)	1.73 (SD = .77; N = 37)	1.13 (SD = .33; N = 40)	1.3 (SD = .62; N = 37)	1.31 (SD = .47; N = 39)	2.08 (SD = 1.19; N = 37)	2.08 (SD = 1.35; N = 39)	3.18 (SD = 1.53; N = 33)
6	1.68 (SD = 1.01; N = 41)	1.92 (SD = 1.06; N = 37)	1.41 (SD = .64; N = 39)	1.61 (SD = .73; N = 36)	1.05 (SD = .22; N = 40)	1.16 (SD = .44; N = 37)	1.28 (SD = .46; N = 39)	2 (SD = 1.2; N = 37)	2 (SD = 1.3; N = 39)	3.06 (SD = 1.62; N = 33)
7	1.59 (SD = .92; N = 41)	1.97 (SD = 1.07; N = 37)	1.31 (SD = .47; N = 39)	1.51 (SD = .69; N = 37)	1.02 (SD = .16; N = 40)	1.31 (SD = .86; N = 36)	1.26 (SD = .5; N = 39)	1.97 (SD = 1.13; N = 36)	1.9 (SD = 1.29; N = 39)	2.82 (SD = 1.57; N = 33)
Mean AUC	11.53 (SD = 5.55; N = 42)	13.79 (SD = 5.69; N = 37)	9.97 (SD = 3.79; N = 41)	12.36 (SD = 4.74; N = 37)	7.03 (SD = 1.79; N = 41)	8.54 (SD = 3.28; N = 37)	8.44 (SD = 3.51; N = 40)	13.43 (SD = 6.79; N = 37)	13.18 (SD = 7.49; N = 40)	20.42 (SD = 8.14; N = 33)
P-value		.1625 (.0458)		.0207 (.0182)		.0167 (.0375)		.0007 (.0004)		.0002 (.0004)

Table 2:

Acute symptoms questionnaire, by trial arm.

These results reflect analysis of those 75% returning questionnaires (39 patients in the HBO arm, 36 patients in non-HBO arm). The p-values are from the joint structural equations model that includes Comfort at day 8; robust standard errors were used because of differences in variance and departures from Normality. Univariate Mann-Whitney p-values are also therefore displayed, in brackets.

Assessment	HBO	Non-HBO	Difference (HBO minus Standard) in fitted means
Baseline	.164 (SD =.213) Median =.063 IQR = .011 to .234 N = 67	.232 (SD =.289) Median = .074 IQR = .02 to .389 N = 69	-.075 (95% CI: -.15 to -.001) P = .046
3 months	.115 (SD =.199) Median =.02 IQR = 0 to .168 N = 46	.18 (SD =.232) Median = .04 IQR = .011 to .38 N = 55	-.057 (95% CI: -.115 to 0) P = .049
6 months	.116 (SD =.206) Median =.02 IQR = 0 to .106 N = 51	.153 (SD =.232) Median = .03 IQR = .011 to .21 N = 54	-.06 (95% CI: -.121 to 0) P = .049
12 months	.111 (SD =.179) Median =.021 IQR = 0 to .168 N = 44	.252 (SD =.299) Median = .101 IQR = .011 to .441 N = 48	-.076 (95% CI: -.151 to -.001) P = .048

Table 3 : Visual analogue pain scores at each time point

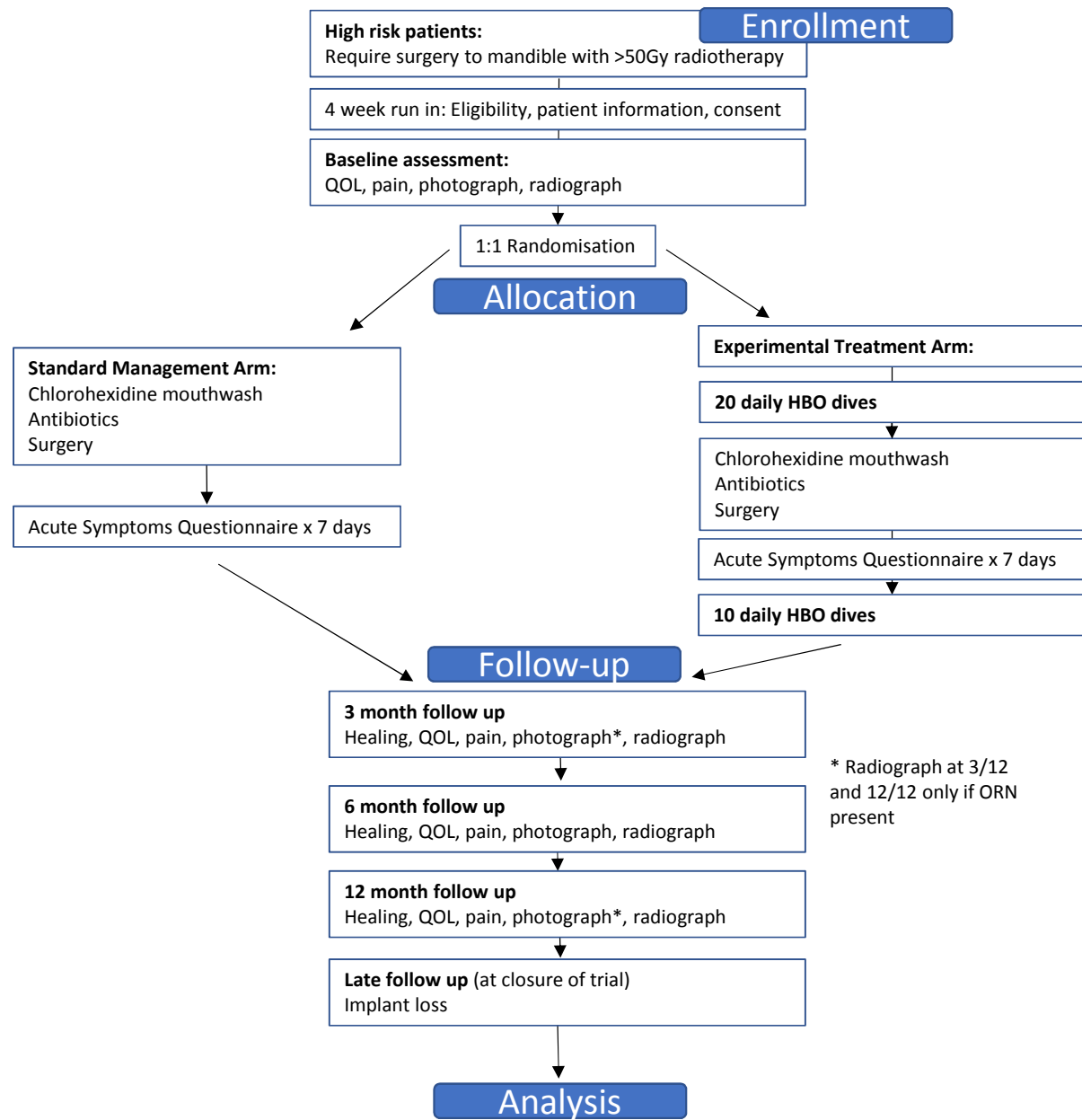
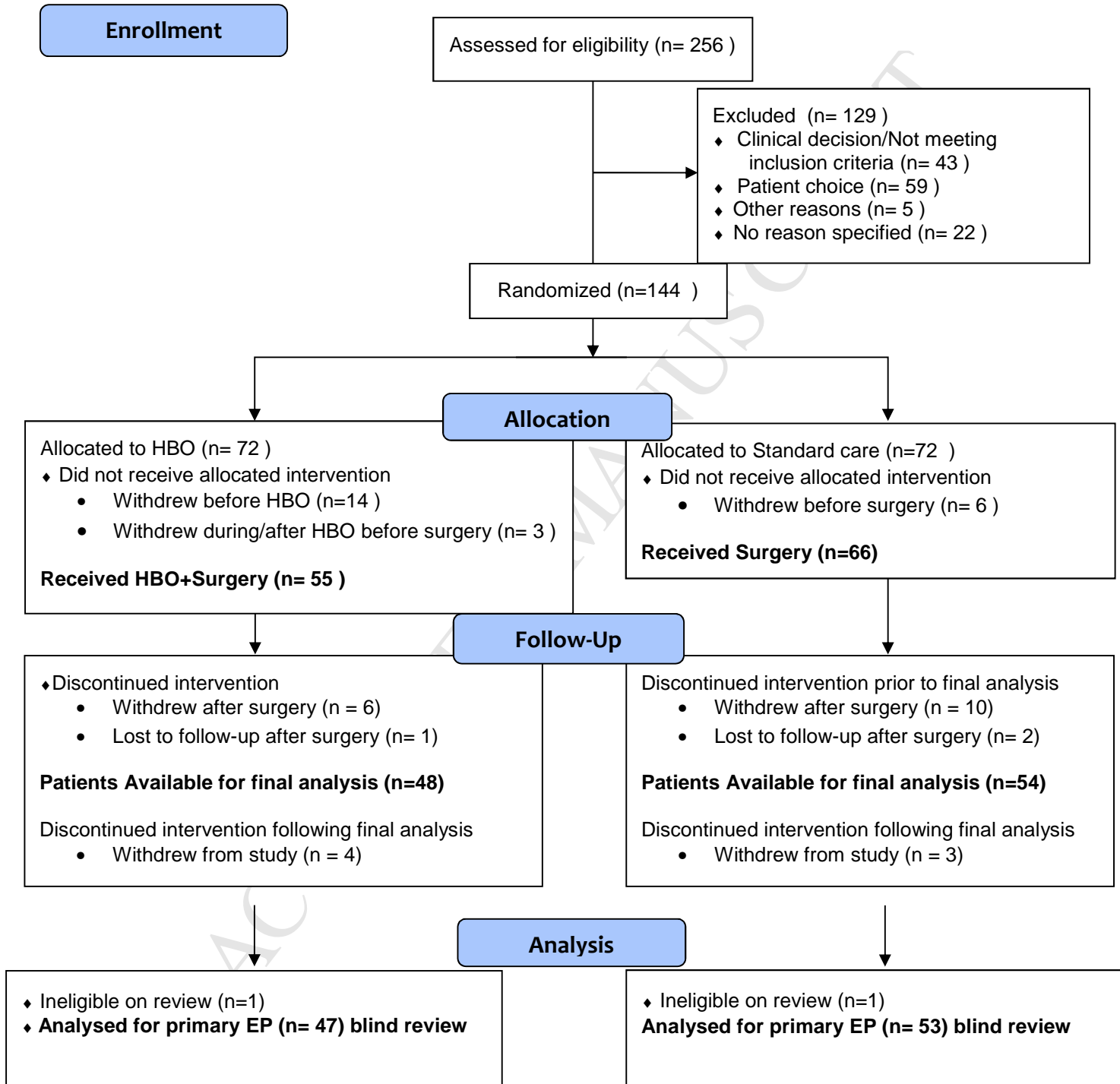
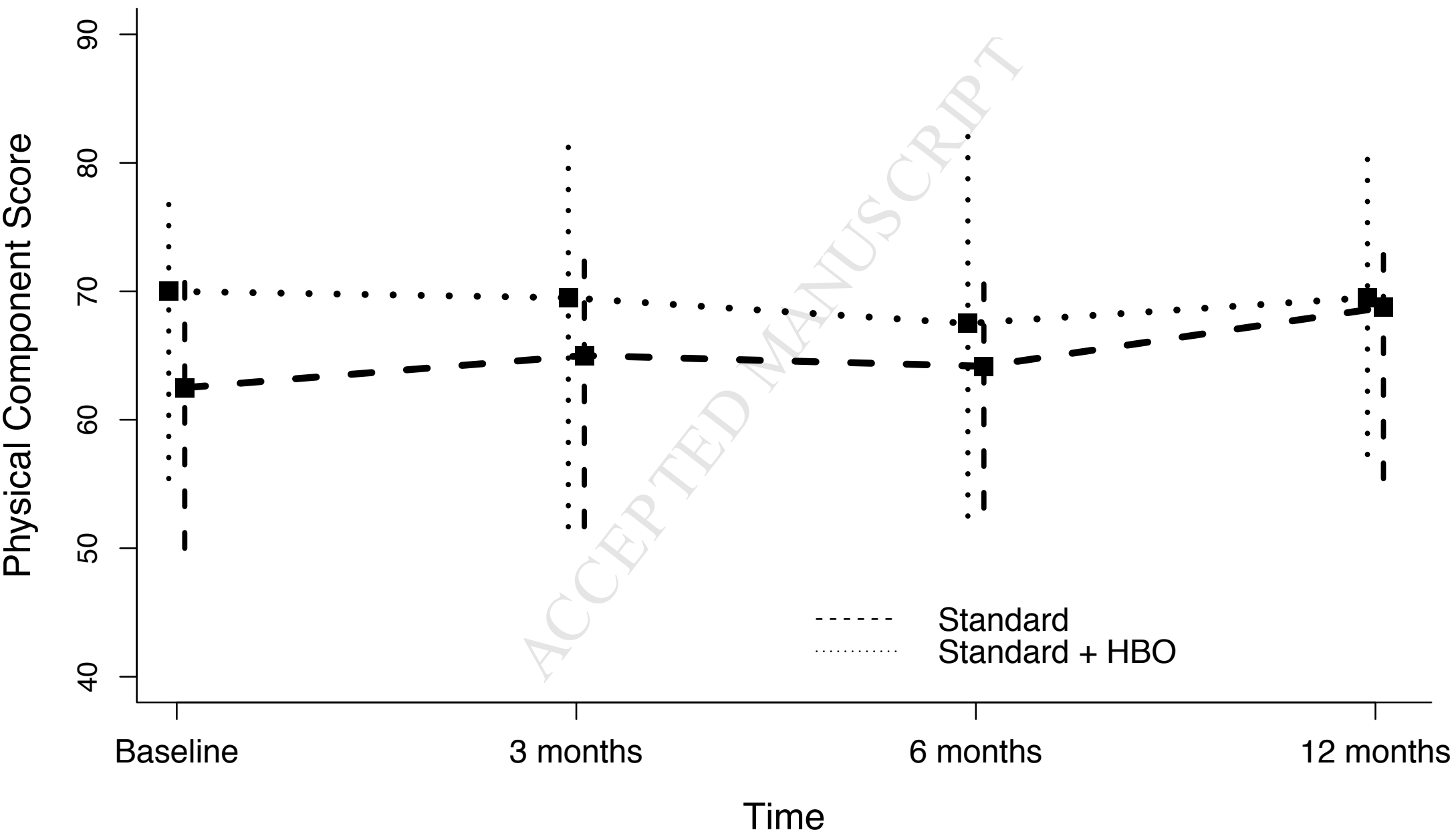
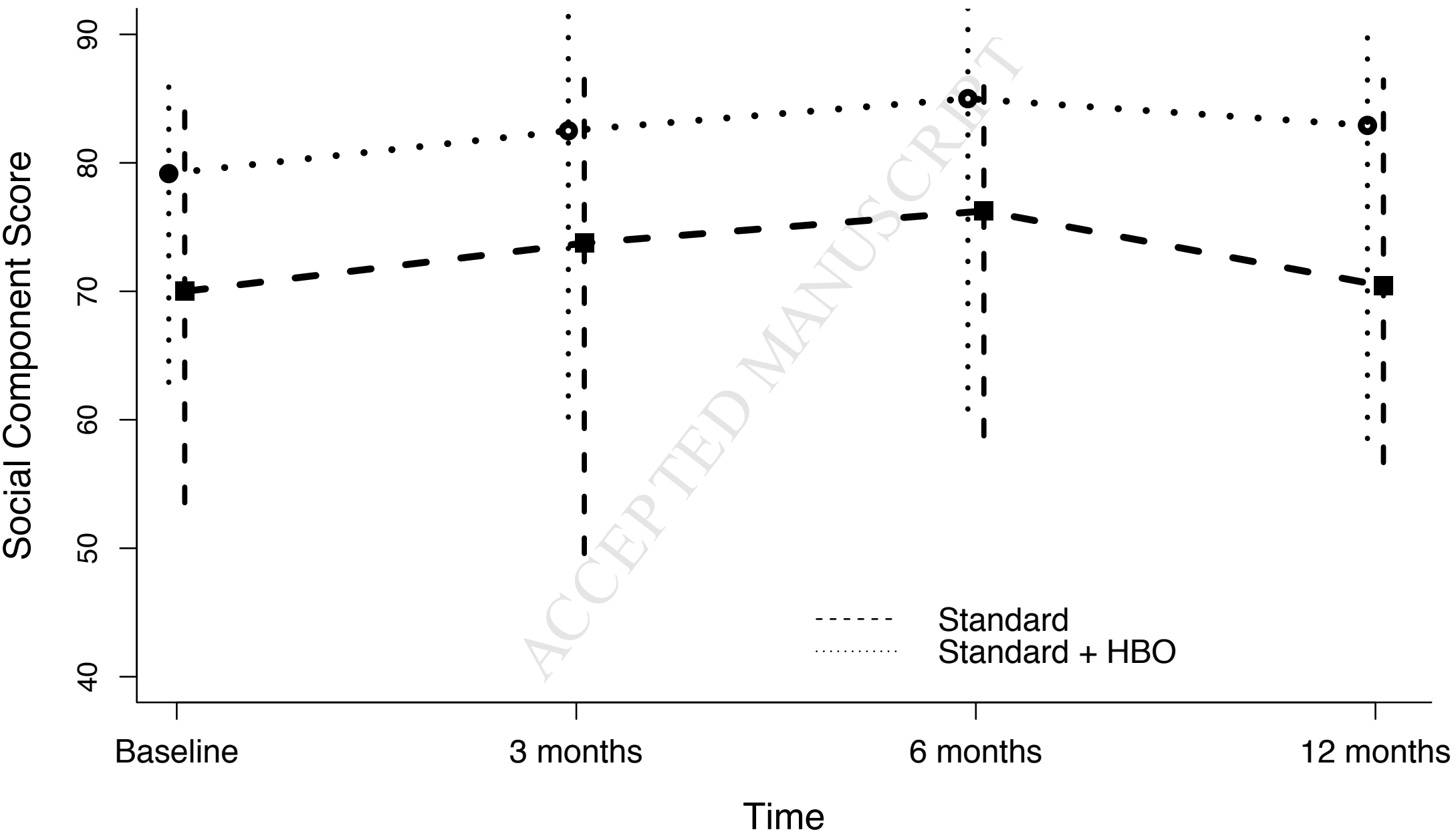


Figure 2: Consort diagram













**Summary:**

The results of this multicentre randomized controlled trial refute earlier positive results for hyperbaric oxygen therapy in the prevention of mandibular osteoradionecrosis. Both arms had a very low rate, overall 6%, of osteoradionecrosis. This is only the second randomized trial carried out in this setting, and the only one in the era of modern radiotherapy techniques. Our results suggest the continued widespread prescription of HBO in prevention of mandibular osteoradionecrosis is not justified.